

Developing Pattern Recognition in Insomnia

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Learning objectives

- Understand the physiology of sleep pertinent to the clinical evaluation of insomnia.
- Practice the clinical evaluation of insomnia using history to elucidate relevant patterns.
- Recognize specific sleep-related problems which present as insomnia, and review the treatments for these conditions.

Agenda

- 10 minutes: Introduction & physiology
- 10 minutes: Common patterns #1
- 15 minutes: Practice cases #1
- 10 minutes: Common patterns #2
- 15 minutes: Practice cases #2
- 15 minutes: Review
- 10 minutes: Evaluations

INTRODUCTION & PHYSIOLOGY

Background

- Definitions vary (symptom v. diagnosis)
Dissatisfaction with quantity or quality of sleep obtained, despite attempts to sleep
- Common condition, often chronic
- Bothersome; cause of suffering
- Teaching on insomnia is often limited to:
 - 1) Sleep hygiene measures
 - 2) Sedating medications (trazodone, TCAs)

Analogy: Chronic Pain

- Etiology
 - often not apparent in chronic cases
- Associations
 - Suffering, depressed mood, impaired function
 - Requests for & expectation of relief - hard to meet
- Tx can be unsatisfying for patient & physician
 - Success rate low
 - Options seem limited, of low utility, unappealing
 - Medications: potential for harm, dependence
 - Non-medication: often depend on motivated patient

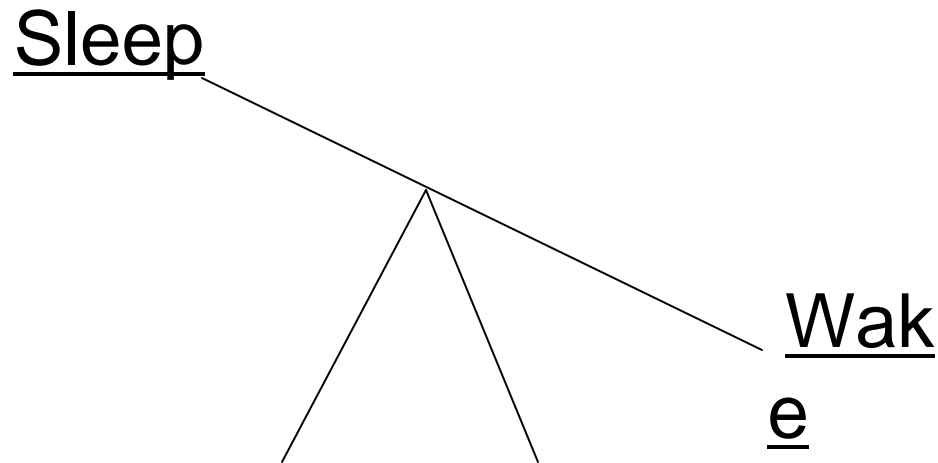
Insomnia: perspective matters

- Seen as: “not enough sleep”
 - Solution seen as “more sleep”
 - Irony: trying to sleep increases wakefulness
- Actually: “too alert” (“too much wakefulness”)
 - Wakefulness at times when sleep is desired
 - Wake/arousal intruding on sleep/sleepiness
- (Can also contribute: “expectations not realistic”)

Sleep/wake goals & drives

	Internal drive: Sleep	Internal drive: Wake/Alert
Attempting: Sleep	Desired sleep	Insomnia
Attempting: Wake	Drowsy wakefulness	Desired alert wakefulness

Schema: Normal Sleep-Wake Cycling



Timing:

- (1) Circadian rhythm
- (2) Homeostasis
- (3) Purposeful behavior

Neurotransmitters mediating sleep & wakefulness

- Sleep-promoting
 - GABA
 - Adenosine, Galanin, GHRH, Ghrelin, Serotonin
- Wake-promoting
 - Acetylcholine
 - Glutamate
 - Histamine
 - Hypocretin = orexin
 - Norepinephrine & other catecholamines
 - Serotonin

Evaluation of Insomnia

1) Acute or predictable?

Chronic?

2) Why too alert?

a) Timing of sleep/wake attempted & achieved

b) Hyperarousal

Analogy to Dizziness

- Dizziness: bothersome symptom we're used to evaluating with Hx, & teaching
- Two major categories of cause:
 - Otoneurologic: vertigo
 - Cardiovascular/volume: lightheadedness (presyncope)
 - Also, other causes: anxiety, cervicogenic (absence of above features; can be more nebulous)
- Initial evaluation is HISTORY, HISTORY

Normal sleep-wake timing

- Highest “sleep propensity”
 - #1: Very early AM (“wee hours”)
 - #2: Early afternoon (allows siesta/nap)
- Lowest “sleep propensity”
 - Morning, after awakening (mid-AM)
 - Evening (~3-4 hrs before usual HS)

Timing or Hyperarousal?

- Timing problems readily uncovered by Hx
- Actual sleep/wake cycle \neq desired times
- Two hallmark features:
 - 1) Not sleepy at times when when sleep is desired or socially acceptable **and:**
 - 2) No trouble sleeping at certain other times
(can also be an issue)

Timing or Hyperarousal?

- Hyperarousal underlies the rest of insomnia
- Trick is sorting out why, & what to do for it
- Hallmark features:
 - A) Sleepy when trying to sleep, yet can't; or
 - B) Sleepiness disappears when pt tries to sleep

COMMON PATTERNS #1

TIMING PROBLEMS

Common Patterns of Timing Problems: Phase Shift

Insomnia is always at same end of the
attempted sleep period

and

Difficulty staying awake at the other end

“Phase Shift” Conditions

- Daylight savings time change
- Jet lag
- Later sleep & wake times on weekends

- Shift work
- Night owl = “delayed sleep phase” (incl. teens)
- Early bird = “advanced sleep phase”
- Free running circadian rhythm [1/3 of blind]

Common Patterns of Timing Problems: Fragmented* sleep

Awakens after a few hours of sleep

and

Obtains sleep at other times of day (naps)

*Fragmented over 24-hrs

History for Timing

- Open-ended history may not reveal timing info
- Guide history through 24 hr day: “Tell me about your sleep. When do you go to bed? Are you sleepy then? When do you fall asleep? What happens during the night? ...”
- Goal is to elicit:
 - Timing of sleep attempted, achieved, & desired
 - Timing of wake attempted, achieved, & desired
 - External constraints (job, school, etc)
 - What happens on days off & vacation?
 - Duration of this pattern
- Further data: sleep diary, actigraphy

Approaches for Phase Shift Problems

- Change external constraints (work, school)
- Adjust sleep/wake time (chronotherapy)
 - Adjust toward goal in 15 min/day increments
 - Once at goal, maintain same sleep/wake time!
- Light (phototherapy) at sleepy end of day
 - Evening for: early birds or those traveling west
 - Morning for: night owls or those traveling east
- Melatonin (or ramelteon, \$4/dose)
 - Evening for: night owls or those traveling east

Consolidation of sleep fragmented over 24 hr day

- Goal is to consolidate sleep into one longer stretch, once per 24 hrs
- Mechanism is to increase sleep drive (sleepiness) at bedtime & during sleep period
- Advice (sounds counterintuitive to many people)
 - Do not nap
 - Restrict time spent in bed to 15 min more than total daily sleep time (induce some sleep debt, increases “sleep efficiency”)

COMMON PATTERNS #2

HYPERAROUSAL

Causes of hyperarousal

- Alcohol (arousal occurs hours later, after initial sedation)
- Caffeine or exercise too close to bedtime
- Medications, other drugs

- Stress, worry, rumination, caretaker role
- Psychiatric conditions (mood d/o, PTSD, anxiety d/o)
- Conditioned insomnia

- Medical conditions (asthma, GERD, CHF, BPH, pain...)
- Sleep disorders, esp. RLS, OSA, central sleep apnea
- And, finally: Primary insomnia (24-hr hyperarousal)

Some sleep-impairing drugs

- Alcohol (hours after ingestion)
- Beta blockers (can cause nightmares)
- Beta agonists
- Bupropion
- Caffeine
- Ciprofloxacin
- Corticosteroids (systemic)
- Decongestants
- Diuretics (if dosed late in day)
- Stimulants (licit and illicit)
- Theophylline
- Thyroid preparations (at excess doses)

Restless Legs Syndrome (RLS): Diagnosis is by History

* RLS has 4 key features on history:

- Urge to move the limbs
(with or without sensations)
- Worse in the evening or night
- Worse at rest
- Improves with activity

NIH Panel Consensus Criteria
Sleep Med 2003;4;101-19

Secondary RLS: Associations

In which removal or treatment of the listed condition can result in resolution of RLS:

- **Ferritin < 50**
- Low folate level
- B₁₂ deficiency
- Pregnancy
- Meds: many antidepressants; oral contraceptives; antiemetics; others
- End-stage renal disease - transplant may reduce RLS
- Varicose veins, superficial venous insufficiency -??

Common patterns of hyperarousal insomnia

- High degree of focus on bedtime, clock-watching
 - Suggests conditioned insomnia
- Sleeps better anywhere but usual bed
 - Suggests conditioned insomnia
- Anxiety around or at bedtime, or in bed
 - Consider conditioned insomnia or RLS (or fear of sleep e.g. nightmares or sleep paralysis)

Common patterns of hyperarousal insomnia

- Inability to sit still in PM or lie still once in bed
 - Strongly suggests RLS
- Frequent unexplained awakenings, or nocturia
 - Suggests sleep apnea
- Drinks alcohol to fall asleep, then awakens in early AM
 - Suggests alcohol (withdrawal) as cause of insomnia

Patterns of insomnia timing & hyperarousal conditions

- Difficulty falling asleep*:
 - Ask about limb symptoms (?RLS), clues to conditioned insomnia
- Awakening during the night:
 - Frequent, brief: Consider sleep apnea
 - Awakens once, then awake for a while*: Ask about alcohol at hs, clues to conditioned insomnia
- Early morning awakening*:
 - Probe for depression

*also consider timing problem

REVIEW/CLOSING

History, history, history.

Ask about timing & hyperarousal.

Look for patterns.

Diagnosis & advice based on history.

OK...but what if that doesn't work?

Sleep hygiene advice

- Keep the same bedtime and wake time every day.
- Avoid napping.
- Get exposure to bright light every morning.

- Exercise regularly, but not right before bed.
- Avoid alcohol & nicotine within 4 hrs before bed.
- Avoid caffeine within 6 hours before bed.

- Keep the bedroom dark, quiet, and comfortable.
- Use the bedroom only for sleep and sex.
- Turn the clock so you can't see the time.
- If you can't sleep, get out of bed. Return when sleepy.

What about medications?

- Specific treatments for a few conditions (RLS)
- Whether or not cause is identified & specific approach suggested, some patients simply prefer medication (esp. if comorbid conditions)
- Medications for insomnia improve subjective measures of sleep more than objective measures of sleep (little to no objective effect)
- CBT improves both subjective & objective measures of sleep
 - Studies on conditioned &/or primary insomnia

“Cognitive Behavioral Therapy for Insomnia”

- CBTI shows better efficacy than medications at ≥ 6 wks
- Now recognized in sleep medicine as first-line therapy for chronic insomnia...but hard to access
- Includes sleep restriction therapy, paradoxical intention therapy, cognitive restructuring

Patient resources for insomnia

- <http://www.cbtforinsomnia.com/>
- Hauri & Linde “No More Sleepless Nights” 1996 book; also out on audio CD & as a Kindle book (not CBT, but a good self-help book on insomnia)

FDA-approved sedative-hypnotics

- Melatonin receptor agonist: Ramelteon
- Benzodiazepine receptor agonists:
Zaleplon, zolpidem (& CR), es-zopiclone
- Benzodiazepines: Estazolam, flurazepam, quazepam, temazepam, triazolam
- Barbiturates: Butabarbital, pentobarbital/carbromal, secobarbital
- Tertiary carbinol: ethchlorvynol

Top 10 Rx drugs for insomnia, 2002

Ranking: Walsh Sleep 2004;27:1441-2

Prices: drugstore.com

#	Drug	Cost per #30	Site for sedative effect
1	Trazodone	\$ 12 - 21	Histamine? Serotonin?
2	Zolpidem	\$ 16 - 18	GABA _A
3	Amitryptiline	\$ 4	Histamine
4	Mirtazapine	\$ 46 – 50	Histamine
5	Temazepam	\$ 14 (caps)	GABA (nonspecific)
6	Quetiapine	\$ 69 – 224	Histamine
7	Zaleplon	\$ 13 (caps)	GABA _A
8	Clonazepam	\$ 12 - 14	GABA (nonspecific)
9	Hydroxyzine	\$ 18 - 31	Histamine
10	Alprazolam	\$ 12 - 14	GABA (nonspecific)

Trazodone

- Used in primary care for insomnia [off-label use]; little data
J Clin Psychiatry 2005;66:469-76 2004;65:752-5 [Reviews]
- Mixed serotonin agonist-antagonist, similar to nefazodone
 - 5-HT_{2C} agonist, 5-HT_{2A} antagonist
 - Mechanism of action, details of metabolism not known
- Drug-drug interactions, via CYP3A4
 - Ritonavir & likely indinavir, ketoconazole, itraconazole raise trazodone levels
 - Carbamazepine lowers trazodone levels
 - Trazodone raises levels of digoxin and phenytoin
- Rare but serious side effects: priapism, cardiac arrhythmias
- Can cause anxiety, bad dreams, psychosis; likely via metabolite mCPP (meta-chlorophenylpiperazine)

Trazodone metabolite m-CPP (meta-chlorophenylpiperazine)

- Agonist at 5-HT_{1A} & B, 5-HT_{2A} & C
- Used in research studies on serotonin
 - Worsens anxiety & panic, migraines, obsessive-compulsive behavior
- Designer street drug since 2003-05
 - Users report amphetamine-like effects
 - 800,000 tablets seized in EU in 2006
 - Now banned or scheduled in New Zealand, Denmark, Germany, & Malta
 - Not regulated in U.S.

Bibliography

Medications:

- 1) Most commonly prescribed medications for insomnia
Walsh Sleep 2004;27:1441-2
- 2) Review of studies on trazodone for insomnia:
Mendelson J Clin Psychiatry 2005;66:469-76

Non-medication treatments:

- 3) Two “primary care friendly” CBT sessions were better than medications at 2 weeks & 3 months
Edinger & Sampson Sleep 2003;26:177-82
- 4) Little to no evidence of benefit from giving general sleep hygiene advice
Stepanski & Wyatt Sleep Med Rev 2003;7:215-25